**U of Chicago IRAP Handout**

**January 2016**

**Case 1**

**Presenter:** Vincent Cracolici, MD

**Attending:** Aliya Husain, MD

**Clinical History:** This patient is a 67-year-old Laotian male presenting with chest wall pain and cough of one week duration undergoing excision of a new chest wall mass. He is six years status post thymectomy for WHO type AB thymoma. The specimen is received for intra-operative consultation. Following the intra-operative consultation, coronary artery disease, hyperlipidemia, chronic hepatitis B infection, a 30 pack-year smoking history, hypertension, and questionable type 2 diabetes mellitus as well as myasthenia gravis were noted in the medical record. Additionally, 3 months prior to this case, the patient underwent a deceased donor renal transplant for end stage renal disease of uncertain origin, and was being treated with tacrolimus, mycophenolate, and prednisone for immune modulation.

**Diagnosis:** Extrapulmonary tuberculosis

**Differential Diagnosis:**

Given the history, recurrent thymoma must be considered. The extensive inflammatory infiltrate may suggest a neutrophilic dermatosis or neutrophil predominant leukemia. The acute inflammation would also be seen in a soft tissue infection or abscess.

**Key Features:**

-The lesion features profound acute inflammation characterized by neutrophils and macrophages with cellular debris and few multi-nucleated giant cells.

-The lesion involves bone and skeletal muscle. Some areas also feature neovascularization reminiscent of granulation tissue as well as likely reactive nuclear atypia.

-Notably, the lesion does not feature granulomatous inflammation, caseating or otherwise, nor Langhan’s cells. Immunohistochemistry demonstrates profound AFB positivity.

**Discussion**

-The diagnosis of *Mycobacterium tuberculosis* in tissue has classically relied on detection of caseating granulomatous inflammation, however recent evidence suggests that acute inflammation may play a substantial role in the pathogenesis of this infection, and that immune-suppressed individuals may fail to generate granulomas in tuberculosis infection.

-New models of tuberculosis infection suggest that *M. tuberculosis* infection requires destructive acute immune response leading to early necrosis and subsequent formation of the granuloma. Necrosis and formation of the granuloma are now considered virulence factors promoting bacterial proliferation.

-The granuloma itself is more dynamic than previously thought, and that *M. tuberculosis* infection does not simply tolerate granulomatous inflammation, but actually require phagocytosis and necrosis in order to be virulent.

-Our case demonstrates that predominantly acute inflammation can be seen in patients with tuberculosis. Our patient’s medically induced immune suppression also likely contributed to his lack of granulomatous inflammation.

-Chronic granulomatous inflammation with caseous necrosis is not necessarily universal in tuberculosis histomorphology. Not all immunosuppressed patients with *Mycobacterium* infections are from ‘atypical’ species.

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**Case 2**

**Presenter**: Ernest Chan, MD

**Attending**: Sandeep Gurbuxani, MBBS, PhD

**Clinical History**: The patient is a 58-year-old male with a history of T10 compression fracture status post kyphoplasty. The surgery was complicated by pneumonia, *Clostridium difficile* colitis, groin abscess. At this time, the patient was transferred to the University of Chicago At the time of admission, the patient had fever, back pain, general lymphadenopathy and pruritus.

**Diagnosis**: Favor classical Hodgkin Lymphoma with aberrant expression of multiple T-cell antigens with atypical Langerhans cell proliferation

**Differential Diagnosis**:

Based on the clinical setting:

1. Classical Hodgkin Lymphoma
2. Anaplastic T-cell Lymphoma
3. Peripheral T-cell Lymphoma

**Discussion**:

* Morphology
	+ Lymph node showed thickened capsule with nodular lesions with sclerosing fibrosis, a mixed inflammatory background and an infiltrate of large atypical cells
	+ Nodular accumulations of Langerhans cells
	+ The morphology along with expression of CD30 and CD15 was highly suggestive of involvement by classical Hodgkin lymphoma. However, there was no expression of PAX5. While focal and minimal CD20 expression along with OCT2 expression suggested a commitment to B-cell lineage, several T-cell antigens were also expressed along with the cytotoxic markers evaluated. Therefore, based on the morphology and immunophenotype, two possibilities remained: classical Hodgkin lymphoma and ALCL.
* Immunophenotype
	+ Large pleomorphic cells: CD15 +, CD30 +, CD45-
	+ B-cell Antigens
		- PAX5 -
		- Focal CD20+
		- OCT2+ in a subset of large cells
	+ T-cell Antigens
		- CD3 -
		- CD2+, CD5+, CD4+, CD8 +
		- Perforin+, Granzyme+ and TIA-1 +
* Even though seminal work done by Kuppers and colleagues in the 90s firmly established the B-cell origin of Hodgkin lymphoma cells, the tumor cells have frequently lost their B-cell phenotype
* Weak expression of the B-cell transcription factor PAX5 is retained and permits reliable distinction from some T-cell malignancies that can be associated with a significant inflammatory background
* As exemplified by our case, the picture can be confounded by expression of multiple T-cell and cytotoxic markers in a case that at least morphologically appears to be classical Hodgkin Lymphoma and shows unequivocal expression of CD30 and CD15
* With improved understanding of the biology, morphology and immunophenotype, the category of grey zone lymphomas continues to dwindle. However, as exemplified by our case, there are exceptions that fall in the interface of well-defined entities. At least two such cases were presented at the Society of Hematopathology workshop in 2005 where a definitive distinction could not be made between ALK-negative ALCL and cHL – the so called type II grey zone. OCT2 expression was not analyzed in the cases discussed at the workshop.
* Two possible therapy options were discussed and included targeted anti-CD30 therapy with Brentuximab. Unfortunately the patient succumbed to complications related to multiple infections before therapy could be started

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**Case 3**

**Presenter**: Shiraz Fidai, MD

**Attending**: Peter Pytel, MD
**Cytogenetics:** Carrie Fitzpatrick, PhD

**Clinical History**: This 34-year-old male with HIV/AIDS (CD4 count = 1), poor HAART compliance and alcohol abuse was admitted for painful, draining skin ulcers on both lower extremities of 2 weeks duration and chronic temporal-parietal headache. Chest x-ray showed bilateral airspace opacities and head CT showed cerebral volume loss. He had a left upper extremity lesion for over a year. He denied puncture wounds, drainage, or bleeding from the lesion. No other lesions were present. MRI showed a non-specific heterogeneous enhancing mass.

**Diagnosis**: EBV associated smooth muscle tumor (EBV-SMT)

**Differential Diagnosis**:

Based on the clinical setting: A. Peripheral nerve sheath tumor, B. Mycobacterial spindle cell pseudotumor, C. Kaposi sarcoma – nodular stage, D. Smooth muscle tumor (leiomyoma and leiomyosarcoma)

**Discussion**:

Historical Background:

- First described in 1970 by Pritzker, K.P. as “leiomyosarcomas” developed post-transplant

- Association with EBV made in 1995 in 2 simultaneously published articles in NEJM

- Subsequent case reports and small studies demonstrated visceral organ involvement in unusual sites and multifocal tumors in >50% of the cases

Histologic Features:

- Interlacing fascicles of mild to moderately pleomorphic spindle/ovoid cells with ample eosinophilic cytoplasm – SMA+ and Desmin+

- Can resemble leiomyoma, angioleiomyoma, SMT-UMP, LMS, and myopericytoma

- Less common features include foci of small round cells with irregular nuclear contours with smooth muscle immunophenotype and T lymphocytes infiltrates in tumor

Pathogenesis:

 - EBV infection causes transformation of smooth muscle cells

- Some cases show an increase in CD21, hypothesized as possible receptor for the virus

- Unclear how EBV causes neoplastic transformation but clonal virus proliferation is present and synchronous lesions in same patient have unique EBV clones in each lesion

Molecular Findings:

- No reported recurrent molecular genetic findings described in literature

- In contrast to multiple gene alterations and very complex karyotypes, including numerous chromosomal gains and losses seen in soft tissue leiomyosarcomas, no genomic alterations present in our case via whole genome SNP array

Clinical information:

- Occurs in both children and adults (median age: 30)

- Recent subclassification based on cause of immunodeficiency and most common site of involvement

- HIV: CNS, post-transplant: liver, and congenital immunodeficiency: lungs

- Surgical resection as main treatment and most patients survive with persistent disease (80%); only rare patients die of disease

- HIV-related tumors have worst overall survival

- Prognosis determined by immune condition of patient, not by tumor histology or focality

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**Case 4**

**Presenter**: Jefree Schulte, MD

**Attending**: Ricardo Lastra, MD, Aliya Husain, MD

**Clinical History**: This 40-year-old female (G14P10) with a medical history including anemia and treated Chlamydia and Gonorrhea infections was at 38 weeks 6 days gestation. The fetus had multiple anomalies by ultrasound exam. Following induction of labor, the vaginal delivery was complicated by breech presentation. A representative section of the placenta is provided.

**Diagnosis**:

- Third trimester placenta (280 g) with dysmorphic villi consistent with trisomy 18.

- Retroplacental hematoma (7.5 cm).

- Three vessel cord with recent thrombus in one vessel.

- Rare sickled maternal red cells.

**Differential Diagnosis**:

Chorionic villi

Immaturity

Molar pregnancy

Infection

Placental mesenchymal dysplasia

Chromosomal anomaly

Intrauterine hematoma

- Retroplacental

- Subchorionic

- Subamniotic

**Key Features**:

- Low power demonstrates villi of various sizes with irregular villous contours, syncytial knots and perivillous fibrin.

- Some villi demonstrate prominent stromal overgrowth.

**Discussion**:

Dysmorphic villi

* Nonspecific term with various morphologic findings.
* Features include irregular villous contours, stromal overgrowth, various vascular abnormalities, and increased trophoblastic inclusions.
* Easily confused with entities listed in the differential diagnosis

Clinical Findings

 - Prenatal testing reveals trisomy 18.

Histologic Features

* Well-developed tertiary villi ruled out immaturity.
* Given presentation at full term, and lack of villous cisterns or trophoblastic proliferations, molar pregnancy was no longer considered.
* No viral inclusions or chronic villitis identified, making infection less likely.
* Placental mesenchymal dysplasia not considered due to lack of histologic correlates and low placental weight.

Retroplacental hematoma

* Hematoma confined entirely behind maternal surface and not involving fetal membranes.
* Associated with the worst outcome of all intrauterine hematomas.

Umbilical Cord Thrombus

 - Nonspecific finding, with some evidence of increased associated with trisomy 18.

Sickle cell trait:

 - No increased risk of morbidity to fetus.

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**Case 5**

**Presenter:** Lily Tran, MD

**Attending:** Peter Pytel, MD

**Clinical History:** This 57-year-old male with NF-1 initially presented with hematochezia. He was seen by a gastroenterologist who attributed the bleeding to hemorrhoids. His rectal examination also revealed an enlarged prostate. The patient was therefore referred to a urologist who noticed blood in the patient’s urine. A CT and MRI were obtained which revealed a left renal calculus and a 3.4 cm enhancing mass in the left adrenal gland. He underwent an adrenalectomy. A representative section from the adrenal mass is provided.

**Diagnosis:** Composite tumor with pheochromocytoma and neuroblastoma (aka composite pheochromocytoma)

**Differential Diagnosis:**

* Neuroblastoma
* Pheochromocytoma
* Carcinoid tumor
* Unusual variant vs collision tumor?

**Key Features:**

* Tumor had two distinct morphologies:
	+ The first component had these larger cells with abundant eosinophilic cytoplasm with eccentric and vesicular nuclei and prominent nucleoli. Within this first component also were smaller, more immature-appearing cells. These cells were interspersed within this fine fibrillary matrix. The lesional cells in this component were diffusely positive for PGP9.5 and stained for synaptophysin consistent with a poorly-differentiated neuroblastoma.
	+ The second component contained nests of more epithelioid cells surrounded by this rich capillary network. The cells here stained for chromogranin and synaptophysin. An S100 also highlighted the sustentacular cells. These features were consistent with a pheochromocytoma.
	+ Negative for CAM5.2, arguing against carcinoid tumor

**Discussion:**

* Composite pheochromocytoma is a tumor consisting of combined features of pheochromocytoma and a neural component such as ganglioneuroma, ganglioneuroblastoma, neuroblastoma, MPNST, or neuroendocrine carcinoma.
* Comprises <3% of adrenal and extra-adrenal pheochromocytomas.
* Less than 50 cases have been reported in the English literature, and are often associated with NF1 or MEN2A.
* In most composite pheochromocytomas, the neural component is mainly composed of more mature elements like ganglioneuroma, but our case is very unusual because the neural component had more immature features. This occurrence with neuroblastoma is very infrequent and only 9 cases have been described.
* Pheochromocytoma
	+ Rare benign tumors that mainly occur in adults between 30-50 yo
	+ Arises from chromaffin cells and produce catecholamines
	+ Surgical resection considered curative in most cases
	+ Majority of pheochromocytomas are sporadic
	+ But in 30% of cases, they can be seen in familial disorders
		- MEN 2A/2B
			* *RET*/10q11.2
		- Neurofibromatosis 1
			* *NF1*/17q11
		- von Hippel-Lindau disease
			* VHL/3p25-26
		- Hereditary pheochromocytoma syndrome
			* Succinate dehydrogenase
* Neuroblastoma
	+ Malignancy of the autonomic ganglion cells
	+ Approximately 90% of patients diagnosed before 5 yrs of age
	+ Surgical resection is used to manage the low-stage neuroblastoma
	+ Chemotherapy is used in the more advanced stages of the disease
	+ Prognosis in those with neuroblastoma depends on
		- Age at diagnosis
		- Grade and stage of the tumor
		- N-myc amplification status
* Not apparent how the neuroblastic component impacts the therapeutic modality and prognosis when compared to ordinary pheochromcytoma.
* Interesting aspects in our case
	+ Both components in this patient’s tumor had same chromosomal gains and losses
	+ No N-myc amplification
	+ Cytogenetics profile and the patient’s clinical setting were more consistent with a pheochromocytoma, suggesting patient’s tumor will behave more like ordinary pheo
	+ Another composite tumor from a different patient in our database exhibited features of neuroblastoma with N-myc amplification. The patient was a 5-year-old male who also had bone marrow involvement at diagnosis. The overall picture in this case was more consistent with a neuroblastoma.
	+ The diversity in these two cases suggest that the two components can exist in one tumor in either setting, and that maybe we should apply the clinical context when diagnosing these tumors.

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**Case 6**

**Presenter:** Stephanie M. McGregor, MD, PhD

**Attending:** Husain Sattar, MD

**Clinical History:** The patient is a 67-year-old female with a longstanding history of hypertension and diabetes who presented to a geriatrician to establish primary care. She had no new complaints, but review of systems revealed occasional breast pain. Diagnostic mammogram and ultrasound revealed a mass, which was biopsied.

**Diagnosis:** Metastatic well differentiated neuroendocrine tumor (carcinoid tumor), suggestive of gastrointestinal primary

**Differential Diagnosis:**

* Primary well differentiated neuroendocrine tumor (carcinoid tumor) of the breast

**Key morphologic and immunohistochemical features:**

* Round nests of tumor cells with an organoid appearance and prominent rosettes
* Small nuclei with smooth nuclear membranes and finely stippled chromatin
* Striking eosinophilic granules that are subnuclear in localization
* Rare mitoses and no necrosis
* Synaptophysin and chromogranin diffusely positive
* Absence of myoepithelial layer (as demonstrated by myosin heavy chain and p63)
* GATA3 and ER negative
* CDX2 positive
* TTF1 negative

**Discussion:**

* Though cases of well differentiated neuroendocrine tumor (carcinoid tumor) primary to the breast have been reported, metastases are much more likely and the identification of such morphology in the breast should prompt a search for a distant primary.
	+ There is no role for mastectomy in the treatment of a metastatic neuroendocrine tumor.
* Multiple features can be helpful to determine if a lesion is primary or metastatic and also to identify the site of the primary.
	+ The presence of an *in situ* component strongly supports a primary lesion.
	+ CK7 and CK20 help to distinguish a primary breast lesion from a gastrointestinal primary; CK7 must be interpreted with caution in distinguishing lung from breast.
	+ Mammary lineage markers (e.g. mammaglobin and GCDFP15) are helpful if positive but lack sensitivity (the expression of GATA3 in cases with neuroendocrine has not been formally evaluated).
	+ ER/PR: Usually strong and diffuse in primary neuroendocrine tumors, but not absolutely.
	+ CDX2 for gastrointestinal primaries (~100% of reported cases)
	+ TTF1 for lung primaries (~60% of reported cases)
* Invasive breast carcinoma can demonstrate focal expression of neuroendocrine markers in up to 30% of cases. Focal expression without the appropriate histologic features (e.g. organoid appearance) is not diagnostic of neuroendocrine tumors.
* The current WHO (2013) divides these cases into three categories that are similar to those used in other organ systems.
1. Neuroendocrine tumor, well-differentiated
	* <1% of breast carcinomas, comparable to carcinoid tumor
2. Neuroendocrine tumor, poorly differentiated/small cell carcinoma
3. Invasive breast carcinoma with neuroendocrine differentiation
	* This category includes both specific categories that frequently demonstrate neuroendocrine differentiation (e.g. solid papillary carcinoma and hypercellular mucinous carcinoma) and invasive carcinoma of no special type; the former lesions should be diagnosed according to overall morphology and not according to the presence of neuroendocrine features.
	* The 2003 WHO classification required at least 50% of tumor cells to express at least one neuroendocrine marker by immunohistochemistry, but given the arbitrary nature of this cutoff, it was eliminated in the latest edition.

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